Carbon Monoxide and Hospital Admissions for Congestive Heart Failure: Evidence of an Increased Effect at Low Temperatures

Robert D. Morris and Elena N. Naumova

Department of Family Medicine and Community Health, Tufts University School of Medicine, Boston, MA 02111 USA

The combined effects of carbon monoxide and low temperature on daily variation in hospital admissions for congestive heart failure (CHF) were examined for a 4-year period in Chicago, Illinois. Medicare hospital admissions for CHF were analyzed as a function of the maximum hourly temperature, maximum hourly levels of carbon monoxide (CO), and other criteria pollutants in Chicago for each day of the 4-year period (1986–1989). The regression analyses for the time series were conducted using single and multipollutant models with interaction terms and adjustments for weather, weekly cycles, seasonal effects, and secular trend. The data were also grouped into three temperature ranges, <40°, 40°–75°, and >75° F, and the relationship between CO and CHF admissions was evaluated for each range. For the 4-year time series, the CO level was positively associated with hospital admissions for CHF in the single pollutant and multipollutant models after adjustment for seasonal effects and weather pattern. The relative risks of hospital admissions for CHF in Chicago associated with the 75th percentile of exposure to CO in the high, medium, and low temperature ranges were 1.02 [95% confidence interval (CI), 0.95–1.10], 1.09 (CI, 1.04–1.14), and 1.15 (CI, 1.09–1.22), respectively. In these data, the effect of CO on hospital admissions for CHF was temperature dependent, with the magnitude of the effect increasing with decreasing temperature. This synergy may help to explain the association between ambient CO and CHF admissions demonstrated in other studies. *Key words*: air pollution, carbon monoxide, elderly, heart failure, Medicare, synergy, temperature, time series. *Environ Health Perspect* 106:649–653 (1998). [Online 14 September 1998] *http://ehpnet1.niehs.nih.gov/docs/1998/106p649-653morris/abstract.html*

Studies of the health effects of air pollution generally seek to isolate the specific health effects of a single air pollutant or group of air pollutants. To accomplish this, researchers use a variety of analytic tools to eliminate the effect of potential confounders. It is possible, however, that environmental stressors may act synergistically with air pollutants to cause morbidity and mortality. In this study, we sought to explore this possibility with respect to the health effects of carbon monoxide (CO) and temperature on cardiovascular disease.

The adverse effects of carbon monoxide have long been recognized (*1*). Its cardiovascular effects have been demonstrated in laboratory (*2,3*) and epidemiological studies (*4,5*). Several recent studies have shown that hospital admissions for cardiovascular disease, particularly congestive heart failure (CHF), increase with increasing ambient CO concentrations (*6–8*).

Exposure to the cold air also has well-documented cardiovascular effects. Numerous studies have shown seasonal increases in cardiovascular disease mortality during the winter and in areas with lower mean temperatures (*9–11*). These increases in mortality probably reflect the increased load on the cardiovascular system associated with peripheral and central cooling.

It is certainly plausible that the stress of cold weather could increase one's sensitivity to the adverse effects of CO. This combined effect could be even more pronounced in a person with underlying cardiovascular disease. In this study we explored the combined effect of cold temperatures and air pollution on hospital admissions for CHF using data from Chicago, Illinois.

Methods

The data set used for statistical analysis consisted of daily counts of hospital admissions for CHF and ambient measurements of CO, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone, particulate matter <10 μm (PM_{10}), temperature, and humidity from Chicago. The data and their analyses are described below.

Outcome measures. The Health Care Financing Administration (HCFA) maintains records on the utilization of inpatient hospital services that are covered by Medicare in a database known as the MEDPAR (Medicare Provider Analysis and Review) file. All admissions for residents of Cook County, Illinois, over the age of 64 with a primary discharge diagnosis of CHF (*International Classification of Diseases*, 9th revision-CM, 428) were selected from the MEDPAR files for the period 1986 through 1989. We determined the number of CHF admissions for each day in the entire 4-year period. For congestive heart failure, MEDPAR records have been estimated to have a sensitivity of 85% and a predictive value of 87% when compared to an independent chart review (*12*).

Errors in diagnosis can occur either when the records list CHF patients with some other diagnosis (false negative) or when they give a diagnosis of CHF to patients with other conditions (false positive). Neither error type is likely to vary with the exposures of interest. The false negative will reduce the number of data points and will widen the confidence intervals around individual statistics. The false positive can either result in an understimate of risk (if the true diagnosis is unrelated to the exposure) or an overestimate of risk (if the true diagnosis is related to the exposure). Given the relatively high predictive value of this diagnosis, it is highly unlikely that this type of bias played an important role in our analysis.

Exposure measures. We extracted ambient air quality data for Cook County from the Aerometric Information and Retrieval System (AIRS), which is maintained by the National Air Data Branch of the U.S. EPA. The CO monitoring network includes eight sites, six of which are located in downtown Chicago (*13*). Hourly measures of CO were obtained for all monitoring sites. The maximum hourly values for these sites were determined, and an average of these maxima was calculated for each day. We used the same approach to describe ambient levels of other pollutants. The Cook County network had only one station where daily measurements of PM_{10} were available. Daily maximum temperature and relative humidity data were obtained from the National Weather Service. In the 4-year period (1986–1989), data were available for 80% of days for PM_{10} and for 100% of the days for other pollutants and for weather characteristics. Ambient levels are an extremely crude measure of personal exposure to air pollutants. The resulting misclassification of exposure will be random and will tend to bias our results toward the null.

Analysis. We generated descriptive statistics for all variables. The linear correlations

Address correspondence to R.D. Morris, Department of Family Medicine and Community Health, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111 USA.

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between temperature and air pollutant concentrations were also calculated. To evaluate the significance of the quadratic and higher order terms in the temperature–pollutant relationship, a generalized additive model (GAM) with the orthogonal polynomial of 6 degrees was performed (*14*).

To investigate the independent effect of ambient pollutant and temperature on CHF admission, we used the generalized linear model (GLM) for time series data as described in detail elsewhere (*6*). To adjust for weekly cycles, seasonal effects, and secular trend, indicator variables for the day of the week, month, and year were included in the model. To account for potential overdispersion related to the Poisson regression, the negative binomial approach for the outcome distribution was performed (*15*). We performed GLMs for each pollutant separately (single pollutant model) and for all pollutants combined (multipollutant model). To determine if there was a lag in the association, GLMs were performed for individual pollutants at lags of 1, 2, and 3 days.

The possible synergy of low temperature and high levels of CO on CHF was evaluated in three ways: 1) inclusion of a variable representing the product of temperature and CO concentration in the GLM, 2) simultaneous analysis of both variables in a GAM to generate an additive surface, and 3) an analysis following stratification according to ambient temperature.

To describe this relationship on a continuous scale, a GAM model with the Loess smoother (*16*) was used to construct an image-plot of the bivariate surface (*14,17*). The surface describes predicted estimates of CHF admissions as a function of temperature and ambient CO levels. This model included the same terms as the multipollutant GLM described above.

Although the surface gives a more complete description of the interactive relationship, it does not provide a simple, quantitative comparison of the CO effect in different temperature ranges. Therefore, possible interactions were also examined using a stratified analysis with the data grouped into three temperature ranges. The cut points for stratification were <40°, 40°–75°, and >75°F and were based on statistical and biological considerations. The groupings correspond to the lowest quartile, the middle two quartiles, and the upper quartile of the temperature distribution. The temperature distribution was binomial with two well-defined modes: 39° and 80°. The choice of cut points was also tested using regression tree analysis (*18*). This model suggested cut points of 45° and 75°. Sensitivity analysis showed that shifting the cut points by 5° in either direction or stratification into quartiles did not alter our basic conclusion. The lower cut point at a daily maximum temperature of 40°F corresponds to a daily average of 32°F in Chicago, a temperature with clear biological relevance. The biological basis for defining an upper cut point is less clear. Research on thermal comfort has described a range of indoor temperatures at which the majority of people feel comfortable, referring to it as the comfort zone (*19*). In defining our highest temperature group, we chose temperatures above the upper end of the comfort zone, 75°F.

For each temperature strata the effect of CO on CHF was evaluated using a GLM and GAM. CHF admissions, predicted by the GAM with the loess smoother, were plotted as a function of ambient pollutant levels for each temperature stratum. Ultimately, any choice of cut points will be somewhat arbitrary, so the stratified analysis should be considered as a complement to the image plot.

Although relative risks are frequently used to describe the effect of an air pollutant based on the results of multivariate modeling, the calculation of a relative risk under these circumstances requires the selection of a single level of exposure. The selection of this value and the resulting relative risk estimate are inherently arbitrary. To better describe the relationship between exposure and risk, relative risks were estimated in relation to the actual probability of exposure. The distribution of measurements for each pollutant within each temperature stratum was divided into 20 quantiles. The relative risk for each quantile was calculated based on the results of the GLM. Relative risks were plotted as a function of exposure percentile.

Temperature alone does not fully describe thermal stress. Therefore, we repeated the above analyses, replacing temperature with wind chill index and effective temperature. The wind chill index is an empirically derived expression that is a function of temperature and wind speed. Effective temperature is a function of temperature and humidity.

Standard regression diagnostics for the GLMs were evaluated. Residuals from the GLMs were checked for autocorrelation. As an additional check, all models were recalculated with an autoregressive component (*20*). The order of the autoregressive component was selected from a full autoregressive model by the Akaike information criteria (*21*). The estimation of the model parameters was implemented by the iterated reweighted least square (IRLS) algorithm (*17*). All analyses were conducted using S-plus (*22*).

Results

Table 1 lists summary statistics for CO, SO_2, NO_2, O_3, PM_{10}, temperature, relative humidity, and CHF admissions. Admission counts ranged from 11 to 74 per day, with an average of 34. Average counts were highest on Mondays (42 ± 10) and lowest on Sundays (25 ± 6). CO also had well-defined day-of-the-week effect with the lowest level on weekends (1.96 ± 0.8) and highest on Fridays (2.76 ± 1.1).

Temperature had correlations with CO, NO_2, SO_2, O_3, and PM_{10} of 0.05, 0.41, 0.03, 0.76, and 0.39, respectively. For CO and temperature, neither the linear nor the quadratic term was significant in the polynomial model. The correlation between temperature and CHF admissions was -0.18.

In the GLM, pollutant levels consistently had their strongest effect on CHF admissions at a lag of 0 days. This effect decayed very rapidly with the introduction of lags of increasing magnitude (from 1 to 3 days). Therefore, lags were not considered in subsequent analyses. The GLMs did not exhibit significant autocorrelation of residuals.

As shown in Table 2, CO was the only gaseous pollutant that was significant in

Table 1. Summary statistics for daily levels of pollutants and daily counts of hospital admissions for congestive heart failure (CHF) in Chicago, Illinois, from 1986–1989

	Minimum	25th Percentile	Median	Mean	75th Percentile	Maximum
CO (ppm)	0.679	1.807	2.316	2.509	3.054	8.698
NO_2 (ppm)	0.013	0.035	0.043	0.044	0.053	0.110
SO_2 (ppm)	0.001	0.017	0.023	0.025	0.030	0.091
O_3 (ppm)	0.002	0.022	0.034	0.039	0.051	0.137
PM_{10} (ppm)	6	28	38	41	51	117
Temperature (°F)	-5	39	56	56	74	103
Humidity (%)	48	83	90	88	96	100
CHF admissions	11	27	33	34	40	74

Table 2. The relative risks and 95% confidence intervals (CI) of congestive heart failure admissions associated with exposure to the 75th percentile of daily maximal pollutant level based on results of single and multipollutant models

	Single pollutant model Relative risk (CI)	Multipollutant model Relative risk (CI)
CO	1.09 (1.06–1.12)	1.08 (1.03–1.12)
NO_2	1.04 (1.01–1.06)	0.97 (0.94–1.01)
SO_2	1.09 (1.05–1.13)	1.02 (0.96–1.10)
O_3	1.03 (0.99–1.07)	1.00 (0.95–1.05)
PM_{10}	1.04 (1.01–1.07)	1.02 (0.99–1.06)

both the single and multipollutant models. The relative risk of CHF admissions associated with exposure to the 75th percentile of CO (as compared to an exposure to a concentration of zero) were 1.09 [95% confidence interval (CI), 1.06–1.12] and 1.08 (CI, 1.03–1.12) in single pollutant and multipollutant models. Inclusion of the interaction term increased these values to 1.10 (CI, 1.05–1.15) and 1.09 (CI, 1.04–1.16), respectively.

Figure 1 shows an image plot of the results of the GAM predicting CHF admissions as a function of temperature and CO level. The plot demonstrates a general pattern of increasing effect of CO on admissions as the temperature decreases.

Using the GLM for CO alone after stratification by temperature, the relative risk of CHF admissions associated with exposure to the 75th percentile of CO were 1.02 (CI, 0.95–1.10), 1.09 (CI, 1.04–1.14), and 1.15 (CI, 1.09–1.22) in the high, medium, and low temperature ranges, respectively. The corresponding values for the multipollutant model were 1.01 (CI, 0.92–1.11), 1.07 (CI, 1.01–1.13), and 1.09 (CI, 1.01–1.18). The results of the GAM for the multipollutant model stratified by temperature as shown in Figure 2 indicate that CHF admissions increased with decreasing temperature.

Figure 3 shows the relative risk associated with the exposure percentiles of CO at specific temperature strata for both the single pollutant and multipollutant model. Figure 3 combines the probability distribution of CO in each temperature strata with the risks associated with those levels of CO in that temperature range. This yields three curves that describe the CO-related risk as a function of the probability of that specific CO level within a given temperature range. For example, in the single pollutant model, the 95th percentile of CO levels when temperatures are below 40° is 4.5 ppm, and based on the GLM, this level of CO has a relative risk for hospital admissions of 1.21. In the temperature range of 40°–75°, the 95th percentile of CO is 4.1 ppm and the relative risk is 1.11. Overall, these curves demonstrate that the majority of the increased risk of CHF admissions associated with ambient CO occurs at temperatures below 40° and that there is minimal effect of CO when temperatures exceed 75°. The replacement of temperature with effective temperature or wind chill index did not substantially alter the above results.

Discussion

These results suggest that the association of ambient CO concentration with the number of hospital admissions for CHF is temperature dependent, increasing with

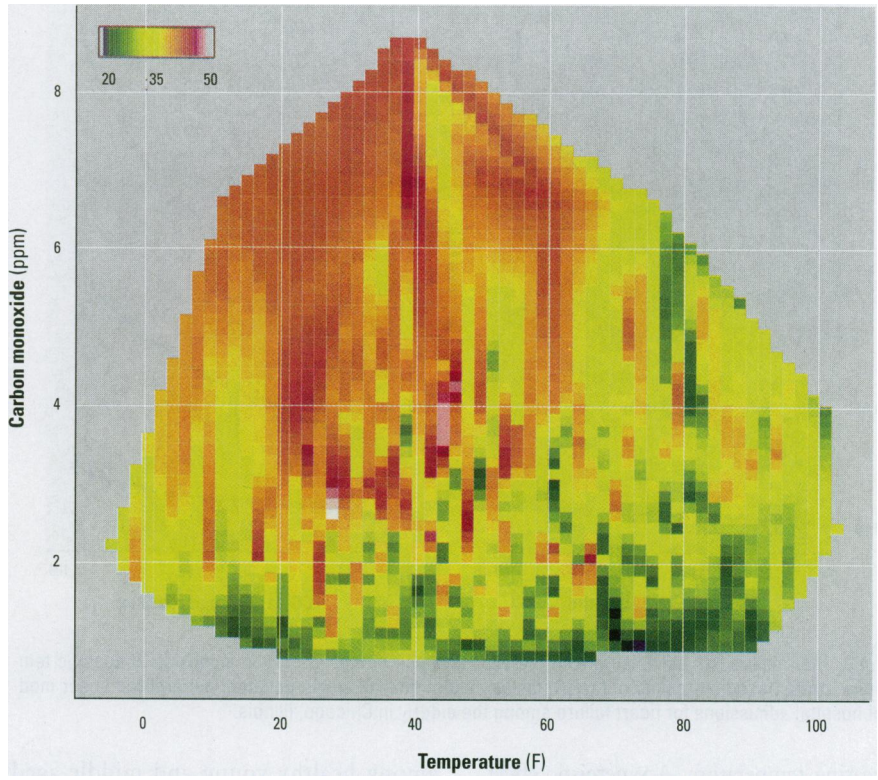

Figure 1. The image-plot of the bivariate surface reflecting the combined effect of carbon monoxide and temperature on hospital admissions for heart failure among the elderly in Chicago, Illinois, constructed by generalized additive model with the Loess smoother.

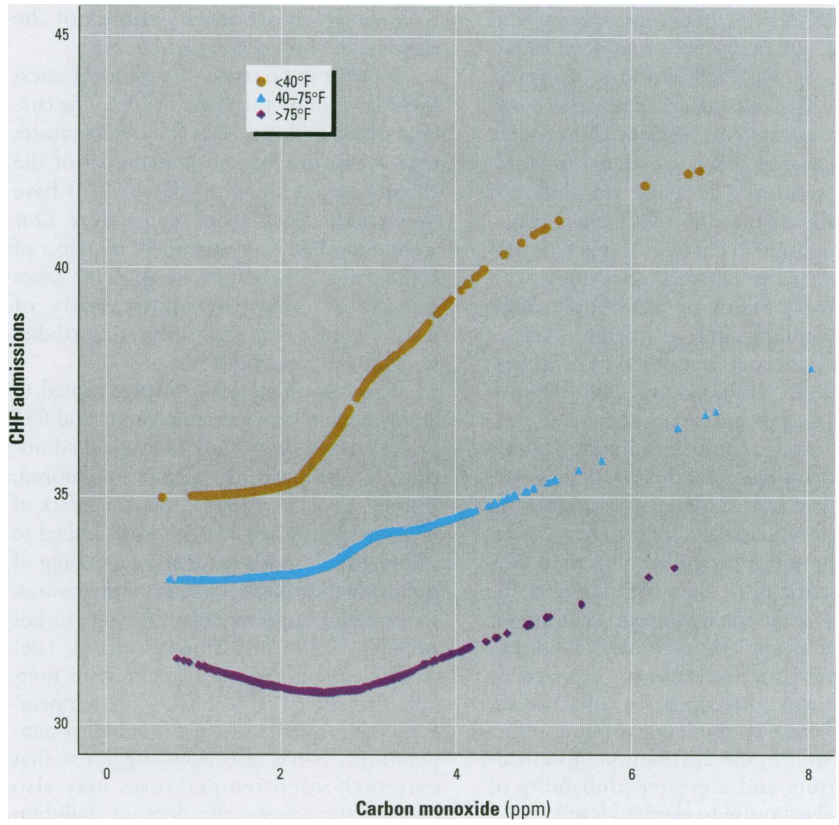

Figure 2. The results of the generalized additive model of hospital admissions for congestive heart failure (CHF) among the elderly as a function of carbon monoxide in Chicago, Illinois, plotted using Loess smoothing after stratification by temperature.

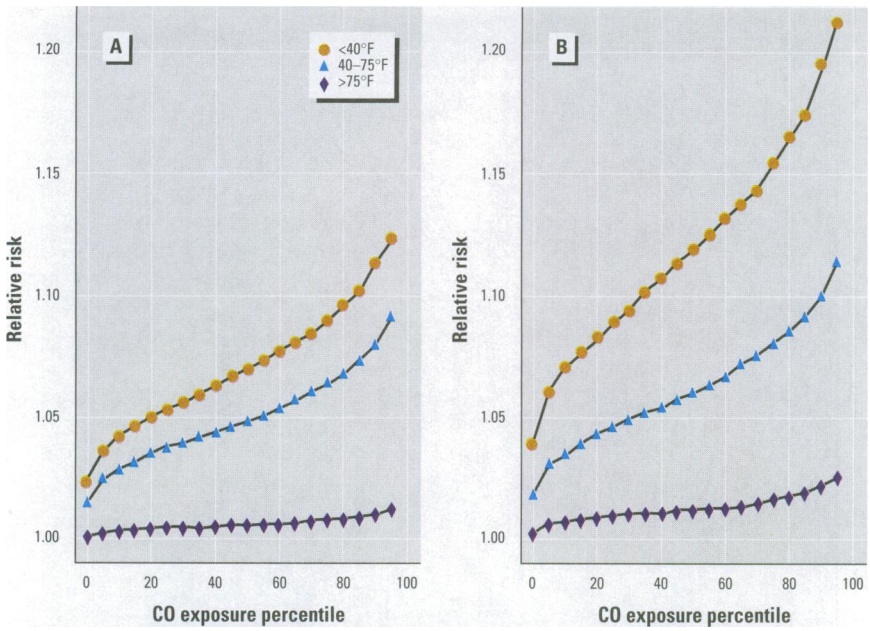

Figure 3. The relative risk associated with the exposure percentiles of carbon monoxide at specific temperature strata based on results of the (A) multipollutant and (B) single pollutant generalized linear models of hospital admissions for heart failure among the elderly in Chicago, Illinois.

decreasing temperature. A synergistic effect of exposure to cold air with CO exposure is biologically plausible and may help to explain the overall association of ambient CO levels with CHF admissions (*6–8*).

An association between ambient CO and CHF admissions has been demonstrated in 8 U.S. cities (*6,8*) and in 10 Canadian cities (*7*). The consistency of this effect suggests that exposure to ambient CO or some exposure that is closely correlated to ambient CO results in an acute worsening of CHF. Any assertion that CO could play a causal role must include an explanation of the fact that the observed association with CHF occurs at levels of CO below current federal standards and well below levels at which effects have been observed in laboratory studies. Several factors could help to explain this apparent inconsistency.

First, levels at ambient monitors poorly represent individual exposures. It is well documented that individual exposures can be far higher than those measured at ambient monitors (*23*), especially those of persons in traffic (*24*). Days with heavy traffic and unfavorable meteorological conditions will increase ambient levels of CO, but can also increase extreme exposures experienced by automobile passengers. In other words, elevated levels at ambient monitors translate to a shift in the distribution of individual exposure and a greater probability of individual exposure to elevated levels.

Second, persons with CHF may be uniquely susceptible to CO. Most studies of the effects of CO have been conducted among healthy young and middle-aged adults. Those studies that have considered persons with heart disease have focused on subjects with coronary artery disease rather than CHF. A review of the literature failed to identify any laboratory studies of the effects of CO on persons with CHF.

Third, the presence of additional stressors may modify the effect of CO. The current study indicates that low temperatures may act in this way. Essentially all of the chamber studies of the effect of CO have been conducted at room temperature. Our study found little or essentially no effect of CO in this temperature range. This raises questions about the applicability of dose–response data from laboratory studies to cold weather conditions.

The epidemiological evidence related to an interaction between temperature and CO is also limited. In a study of hospital admissions for cardiovascular disease in Toronto, Burnett et al. (*25*) found that the effect of CO was weak when analyses were limited to summertime, consistent with our finding of diminished effect at warmer temperatures. In a study of cardiovascular mortality in Los Angeles, California, Shumway et al. (*26*) concluded that the rate of increase in mortality associated with CO at low temperatures was greater than the rate at higher temperatures. It has also been suggested that extremely high temperatures may also increase the adverse effects of air pollution (*27*). The limited data from laboratory studies on the combined effects of air pollution with either heat stress or cold stress seem to support the possibility of enhanced toxicity of CO associated with extreme temperatures (*28*).

Our findings could also be explained by unmeasured covariates that are correlated with temperature. These might include seasonal changes in diet, temporal variation in rates of respiratory infection, or increases in physical stress during the winter months. Without a meaningful surrogate for these exposures, we cannot exclude these covariates as an explanation for the findings of this study.

The assertion that CO and temperature have a synergistic effect on CHF admission rates requires consideration of biological plausibility. Acute heart failure occurs when the load on the heart exceeds its capacity. Both cold and CO can increase the load on the heart. Hence, as discussed below in more detail, cold may modify the effect of CO on cardiovascular morbidity.

Exposure to cold air results in increased heart rate, increased systolic and diastolic blood pressure, and increased cardiac output in young adults (*29–31*). This probably results from sharp increases in sympathetic activity and peripheral vasoconstriction (*32*), a response also seen in subjects with coronary artery disease (*33*) and CHF (*34*). The available research indicates that this increase in blood pressure is greater among older persons (*31,35*). In addition, exposures to temperatures as high as 12°C in still air for as little as 1 hr can induce decreases in rectal temperature (*31,36*) with greater decreases in older men (*35*). Finally, hypoxic conditions will increase the rise in diastolic blood pressure and the degree of shivering associated with cooling (*36*).

Each of these changes will place an increased load on the failing heart. Increased vascular resistance will require increased cardiac work to maintain the same output. Patients using vasodilators may experience blunting of this response, but will then be more susceptible to cooling, which itself can place greater demand on the heart. Shivering in particular will require increased metabolic activity and increased oxygen consumption (*37*). Overall, laboratory studies demonstrate that cooling can increase the workload on the heart and cause oxygen demand to rise substantially (*38,39*). It seems plausible that exposure to cold air would amplify the adverse effects of elevations in carboxyhemoglobin (COHb).

We did not observe an increase in the effect of CO at high temperatures. This may mean that our cut point for the high temperature range was not high enough. It is also possible that Chicago did not experience enough periods of extremely high

temperatures during this time period to allow us to detect an effect. Further studies in areas with higher temperatures will be required to determine if this relationship is "U-shaped."

The impact of CO on CHF patients has not been well studied, but in coronary artery disease patients, this effect has been clearly shown to decrease the time to angina at COHb levels as low as 3.0% (*2*), and perhaps even lower (*3*). It is possible that this threshold for adverse effects may be even lower among persons with CHF than persons with coronary artery disease. Our data indicate that exposure to cold air may reduce this threshold still further. In this way, susceptibility, thermal stress, and relatively low levels of ambient CO may combine to induce acute heart failure at an individual level.

Our study suggests that the effect of CO on hospital admissions for heart failure may be temperature dependent, with the magnitude of the effect increasing with decreasing temperature. This synergy may help to explain the association between ambient CO and CHF admissions demonstrated in other studies. Laboratory studies and further epidemiological studies in other cities with different climates will be required to validate this hypothesis.

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